

A COMPARISON OF CORTISONE AND PREDNISONE IN TREATMENT OF RHEUMATOID ARTHRITIS

A REPORT BY THE JOINT COMMITTEE OF THE MEDICAL RESEARCH COUNCIL AND NUFFIELD FOUNDATION ON CLINICAL TRIALS OF CORTISONE, A.C.T.H., AND OTHER THERAPEUTIC MEASURES IN CHRONIC RHEUMATIC DISEASES*

The object of the therapeutic trial here reported was to determine whether patients with rheumatoid arthritis who had already been treated for at least a year with cortisone acetate would benefit by having their therapy changed to prednisone acetate (delta-1-cortisone acetate).

In total, 68 patients entered the trial, of whom 35, selected at random, had their therapy changed to prednisone acetate and the remaining 33 continued to receive cortisone acetate. Both groups have now completed one year in the trial, and an analysis of the findings during this period is presented below.

Type of Patient.—The patients admitted to the trial were drawn from those with rheumatoid arthritis attending hospital out-patient departments at six different centres. To be included in the trial they had to fulfil three criteria—namely, (a) be more than 16 years of age; (b) be suffering from polyarthritis of a rheumatoid type and no other disease of a serious nature; and (c) have received cortisone acetate or hydrocortisone for at least a year prior to entry.

Allocation of Treatment.—At each participating centre pairs of patients were matched as closely as possible for age, sex, duration of disease, and duration of previous cortisone therapy. One of each pair, selected randomly, continued to receive cortisone acetate; the other was changed to prednisone acetate. (In two instances there were no pairs to patients transferred to prednisone acetate).

Dosage.—The initial dosage of prednisone acetate was one-third of the cortisone acetate dosage that the patient was receiving at entry; subsequently it was adjusted to the individual patient to obtain maximum benefit without side-effects.

Assessments.—Clinical assessment of each patient was required on entry to the trial and at four weekly intervals thereafter. It included a judgment of the activity of the disease, and an evaluation of the patient's general functional capacity. The strength of grip in each hand was measured and laboratory tests were carried out with respect to blood sedimentation rate and haemoglobin level. Any complications or side-effects occurring during the previous four weeks were noted, and other information routinely recorded included blood-pressure reading and the current use of analgesics by the patient.

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Results

Of the 68 patients admitted to the trial, 33 were allocated to continued cortisone therapy and 35 to treatment with prednisone acetate. A comparison of the two groups at entry (Table I) reveals close similarity.

TABLE I.—Number of Patients in the Two Treatment Groups at Start of Trial by (a) Age and Sex, (b) Disease Duration, and (c) Duration of Previous Cortisone (or Hydrocortisone) Treatment

Age (Years)	No. of Patients			
	Male		Female	
	Cortisone	Prednisone	Cortisone	Prednisone
Under 30	0	3	3	2
30-	1	1	2	3
40-	4	6	8	8
50-	6	4	6	8
60-69	1	0	2	0
Total	12	14	21	21

Disease Duration (Years)	No. of Patients		Duration of Previous Cortisone Treatment (Years)	No. of Patients	
	Cortisone	Prednisone		Cortisone	Prednisone
Under 5	5	5	1-	10	14
5-9	13	15	2-	9	9
10+	15	15	3+	14	12
Total	33	35	Total	33	35

During the succeeding 12 months the clinical conditions of 6 patients (5 cortisone, 1 prednisone) led to changes from their allocated therapy and a further 3 patients (2 cortisone, 1 prednisone) died. Relevant details of these deaths and treatment changes are as follows:

Deaths.—(1) Male aged 61 (cortisone): Died (week 3) after an operation for perforated duodenal ulcer complicated by haemorrhage. (2) Female aged 53 (cortisone): Sudden death (week 26) from subarachnoid haemorrhage. (3) Male aged 28 (prednisone): "Died of asphyxia (week 10) and at post-mortem was found to have honeycomb lungs."

Changes of Treatment.—(1) Male aged 42 (cortisone): Changed to prednisone (week 24) "Because symptoms could not be controlled." (2) Female aged 27 (cortisone): Therapy discontinued (week 27). "Sudden onset of substernal pain radiating to neck and shoulder . . . dissecting aneurysm of aorta." (3) Male aged 52 (cortisone): Therapy discontinued (week 32) owing to appearance of amyloid disease. (4) Male aged 54 (cortisone): Changed to prednisone (week 37) after developing congestive cardiac failure. (5) Female aged 35 (cortisone): Severe bilateral scleritis (week 46). Therapy changed to adrenal stimulation and subsequently to prednisone. (6) Male aged 44 (prednisone): Was put on cortisone for three weeks (weeks 39-41) by his own doctor after running out of trial tablets.

After these changes of treatment assessments continued to be made for all except the patient with amyloid disease who, after week 32, was unable to attend hospital. In the analyses that follow, the other five patients have been retained in their original starting groups throughout the year.

Clinical Assessment of Disease Activity

The clinical assessments of disease activity are presented in Table II. By definition all patients were suffering from active rheumatoid arthritis on entry, and the two treatment groups had similar numbers of patients with slightly, moderately, or very active disease. After four weeks of treatment a definite improvement was evident among the patients receiving prednisone. The number with only slight disease activity increased from 19 to 27 and a further 3 were in complete remission. This initial improvement was maintained at 12 weeks, but thereafter there were clear signs of a falling back. Thus, while at the end of the year the number of patients in remission had increased to 5, the

TABLE II.—Number of Patients with Given Grades* of Disease Activity at Different Stages of Trial

Time of Assessment	Treatment Group	No. of Patients					
		Grade				Dead	Total
		0	1	2	3		
Week 0	{ Cortisone Prednisone	0 0	15 19	17 15	1 1	— —	33 35
" 4	{ Cortisone Prednisone	0 3	15 27	16 5	1 —	1 —	33 35
" 12	{ Cortisone Prednisone	0 3	12 27	16 4	4 —	1 1	33 35
" 24	{ Cortisone Prednisone	0 4	13 20	16 9	3 1	1 1	33 35
1 year	{ Cortisone Prednisone	0 5	13 18	13 11	4 —	2 1	32† 35

* Grading of disease activity: 0=none; 1=slight; 2=moderate; 3=severe.

† No assessment available for one cortisone patient.

number with only slight activity had fallen to 18 and the number with moderate activity had risen to 11—compared with 15 originally and only 4 at week 12. The cortisone group, on the other hand, showed no improvement at any stage during the year and there was even some evidence of deterioration in the slightly increasing number of patients assessed as having very active disease.

General Functional Capacity

At the start of the trial there was little difference between the cortisone and prednisone groups in their distribution over four arbitrary grades of functional capacity (Table III).

TABLE III.—Number of Patients with Given Functional Capacity* at Different Stages of Trial

Time of Assessment	Treatment Group	No. of Patients					
		Functional Capacity				Dead	Total
		1	2	3	4		
Week 0	{ Cortisone Prednisone	2 4	18 20	12 9	1 2	— —	33 35
" 4	{ Cortisone Prednisone	2 9	16 22	13 3	1 1	1 —	33 35
" 12	{ Cortisone Prednisone	1 8	17 19	12 5	2 2	1 1	33 35
" 24	{ Cortisone Prednisone	1 9	18 18	12 6	1 1	1 1	33 35
1 year	{ Cortisone Prednisone	2 8	16 20	9 4	3 2	2 1	32† 35

* Functional capacity grades were:

1. Fully employed or employable in usual work and able to undertake normal physical recreations.
2. Doing light or part-time work. Only limited physical recreations. For housewives all except the heaviest housework.
3. Not employed and unemployable. No physical recreations. Housewives only light housework and limited shopping.
4. Confined to house or wheel-chair but able to look after themselves in the essentials of life.
5. Completely bedridden.

† No assessment available for one cortisone patient.

No patients in either group were in grade 5—that is, completely bedridden—at any stage of the trial. Their subsequent progress revealed some degree of improvement in the prednisone group, in the numbers of patients reaching the highest functional grading—that is, fully employable; 4 of the 35 patients were capable of full activity on entry to the trial, 9 after four weeks' treatment, and 8 at the end of the year. The group remaining on cortisone showed no significant changes.

Strength of Grip

The strength of grip of each hand was measured by the patient squeezing an oblong rubber bag, 5 by 3 in. (12.5 by 7.5 cm.) inflated at a pressure of 10 mm. Hg. The average levels of the two groups were almost identical at the start of the trial, but, while there was subsequently no material change in the level of performance by the cortisone group, there was a very definite improvement among the patients receiving prednisone therapy (Table IV). This improvement was evident four weeks after the change-over

TABLE IV.—Average Measurements of Strength of Grip (mm. Hg)

	Treatment Group	Average Measurement				
		Week 0	Week 4	Week 12	Week 24	1 Year
Strength of grip (mm. Hg):						
Left hand	{ Cortisone Prednisone	136 136	140 174	135 173	126 168	137 155
Right	{ Cortisone Prednisone	135 137	142 179	138 184	125 170	129 158

TABLE V.—Number of Patients with Given Strength of Grip (Left Hand) at End of One Year Related to Their Strength of Grip (Left Hand) at Start of Trial

Strength of Grip (in mm. Hg) at Start of Trial	Treatment Groups and No. of Patients	Strength of Grip (mm. Hg) at End of One Year			
		< 50	50–	150–	250+
< 50	{ 0 Cortisone 3 Prednisone	— —	— 3	— —	— —
50–	{ 17 Cortisone 17 Prednisone	4 —	12 10	1 7	— —
150–	{ 10 Cortisone 9 Prednisone	— —	1 3	8 4	1 2
250+	{ 3 Cortisone 4 Prednisone	— —	— 1	1 1	2 2
Total	{ 30 Cortisone 33 Prednisone	4 0	13 17	10 12	3 4

and was maintained at week 12. Thereafter there was some loss of this initial gain, but at the end of the year the strength of grip of prednisone patients still remained, on average, appreciably above their starting level. Table V gives the number of patients with different levels of strength of grip (left hand) at the start of the trial and at one year. A similar pattern was displayed by the data for the right hands.

Blood Sedimentation Rate and Haemoglobin Level

Neither in blood sedimentation rate nor in haemoglobin level did the cortisone group reveal any appreciable change during the year (Table VI). An improvement in both was evident for the prednisone group. Thus the average blood sedimentation rate (mm./hr.) of the group was 37 at the start of the trial and less than half this figure after four weeks' prednisone treatment. This improvement was not, however, maintained during the second six months of the trial, though the average E.S.R. at one year (24 mm./hr.) remained below the initial level.

A similar pattern was evident in the trends of the average haemoglobin level for the prednisone group; an initial rise

TABLE VI.—Average Measurements of (a) Blood Sedimentation Rate and (b) Haemoglobin

	Treatment Group	Average Measurement				
		Week 0	Week 4	Week 12	Week 24	1 Year
E.S.R. (mm./hr.)	{ Cortisone Prednisone	34 37	30 17	28 16	29 19	31 24
Hb (g./100 ml.)	{ Cortisone Prednisone	12.7 12.5	12.9 13.4	12.8 13.5	12.7 13.4	13.1 13.0

TABLE VII.—Number of Patients with Given Blood Sedimentation Rates at One Year Related to Their Rates at Start of Treatment

E.S.R. (mm./hr.) at Start of Treatment	Treatment Group and No. of Patients	E.S.R. (mm./hr.) at One Year			
		< 20	20–	40–	60+
< 20	{ 6 Cortisone 7 Prednisone	4 5	2 1	— 1	— —
20–	{ 15 Cortisone 16 Prednisone	6 11	6 5	2 —	1 —
40–	{ 7 Cortisone 7 Prednisone	1 3	2 3	3 1	1 —
60+	{ 2 Cortisone 4 Prednisone	— 1	1 —	— 1	1 2
Total	{ 30 Cortisone 34 Prednisone	11 20	11 9	5 3	3 2

from 12.5 g./100 ml. to 13.5 g./100 ml. was followed by a fall during the second six months to 13.0 g./100 ml. at the end of the year.

Looking beneath the E.S.R. averages to individual levels the difference between the two treatment groups was again apparent (Table VII). Taking under 20 mm./hr. as a normal level, 20 of 34 prednisone patients, compared with 11 of 30 cortisone patients, had a normal E.S.R. at one year, while 9 and 11 respectively had an elevated rate (20-39) and 5 and 8 had a considerably elevated rate (40 or over).

Dosage

The average levels of cortisone and prednisone dosage are given in Table VIII together with information on the use of analgesics by the two groups of patients. Prior to

TABLE VIII.—*Treatment: (a) Average Dosage of Cortisone and Prednisone at Different Stages of the Trial, and (b) Usage of Analgesic Tablets*

	Treatment Group	Week 0	Week 4	Week 12	Week 24	1 Year
Average dosage (mg./day)	Cortisone	64*	62	65	65	60
	Prednisone	62*	20	17	15	14
Analgesics (average No. of tablets/day)	Cortisone	7	7	6	7	6
	Prednisone	6	3	2	3	4

* Both groups receiving cortisone at week 0.

the start of the trial both groups had been receiving an average dose slightly above 60 mg. of cortisone daily. For the cortisone group this level was maintained throughout the year of the trial. The average daily dose of prednisone administered during the first months was 20 mg., but during later months this level was reduced, reaching 14 mg. at the end of the year.

There was no change in the average number (6-7 daily) of analgesic tablets taken by cortisone patients during the year, while for prednisone patients there was a decline from 6 daily tablets at the start of the trial to 2 a day at week 12. Thereafter their use of analgesic tablets began to increase, and at one year the average figure was 4 tablets a day.

Radiographic Findings

X-ray films of hands and feet taken at the beginning and after one year were available for 51 patients. Of 24 cortisone patients, 10 (42%) had evidence of advance in bony erosion; and of 27 prednisone patients, 9 (33%) showed similar evidence.

Complications and Side-effects

During the year of the trial the following intercurrent illnesses were noted (in addition to those already recorded above under "deaths" and "treatment changes").

1. Female aged 56 (cortisone): Duodenal ulcer (week 15).
2. Male aged 51 (prednisone): Gastric ulcer week 8. This patient had a history of perforated duodenal ulcer 27 years previously.
3. Female aged 32 (prednisone): Gastric ulcer with repeated haematemesis necessitating partial gastrectomy (week 12).
4. Male aged 44 (prednisone): Recurrent cholecystitis, operation week 52.

Two further patients, both on prednisone, showed a rapid and unexplained fall in haemoglobin level during the second quarter of the year.

At each attendance physicians were asked to record the presence or absence of the specific side-effects detailed in Table IX. Patients in the cortisone group showed no change in incidence, while for prednisone patients the most marked change was the increased incidence of "moonface" from 11 cases at week 0 to 19 at week 12 and 20 at the end of the year. There was also some increase in the number of patients with dyspepsia, and, in the first month only, with euphoria. The high recorded incidence of oedema among prednisone patients at week 0 may have

TABLE IX.—*Number of Patients with Given Side-effects at Different Stages of the Trial*

Time of Assessment	Treatment Group	Dyspepsia	Moon-face	Acne	Hirsuties	Oedema	Euphoria	Depression
Week 0	Cortisone	11	12	0	1	4	0	2
	Prednisone	5	11	4	3	11	1	4
" 4	Cortisone	11	12	0	1	2	0	0
	Prednisone	8	12	4	3	4	7	2
" 12	Cortisone	12	11	0	1	2	0	2
	Prednisone	6	19	4	3	2	0	1
" 24	Cortisone	12	13	0	0	5	0	1
	Prednisone	10	20	4	1	2	0	2
1 year	Cortisone	10	10	0	0	2	0	3
	Prednisone	7	20	1	2	4	0	1

been partly due to retrospective recording in that some patients after four weeks' treatment with prednisone were found at week 4 to be pleased with the disappearance of a postural oedema which had not been noted on entry to the trial.

At the start of the trial 12 cortisone patients and 13 prednisone patients were recorded as having a diastolic blood pressure of 90 mm. Hg or over. For all except 6 (3 on each treatment) the diastolic pressure remained at this level at the end of the year (or when the patient was lost sight of). Of the remaining 21 cortisone patients and 22 prednisone patients with an initial diastolic pressure reading of less than 90 mm. Hg, 10 cortisone (48%) and 15

TABLE X.—*Number of Patients with Recorded Increases in Diastolic Blood Pressures (a) to 90 mm. Hg and Above, and (b) to 100 mm. Hg and Above*

Treatment Group	No. Below Given Level at Start of Trial	No. Showing Rise Above Given Level	
		At Any Time During Year	At End of Year
(a) 90 mm. Hg:			
Cortisone ..	21	10 (48%)	1 (5%)
Prednisone ..	22	15 (68%)	6 (27%)
(b) 100 mm. Hg:			
Cortisone ..	26	7 (27%)	2 (8%)
Prednisone ..	32	10 (31%)	5 (16%)

prednisone patients (68%) had recordings above this level at some time during the year, and 1 (5%) and 6 (27%) respectively at the end of the year (Table X). This apparent difference between the treatment groups with respect to rising blood pressure was, however, slight when the arbitrary level was raised to 100 mm. Hg.

Summary

Sixty-eight patients suffering from rheumatoid arthritis who had been taking cortisone acetate for one year or more were divided into two equivalent groups. Thirty-five were transferred to prednisone therapy, while the remainder continued to take cortisone. Both groups were followed for a year.

Throughout the year of the trial the patients remaining on cortisone showed, on the average, no material change for better or worse. The prednisone group, on the other hand, showed improvement in the following characteristics—strength of grip, blood sedimentation rate, haemoglobin level, general functional capacity, and disease activity. At the end of the year the disease was judged to be inactive in five of this group but in none of the patients on cortisone.

The benefit to the patients on prednisone was most marked in the first three months. For the group as a whole it gradually diminished thereafter, though it still remained, to a lesser degree, at the end of one year. This partial loss of initial improvement was accompanied by, and may have been partly due to, a reduction of prednisone dosage during the year. The dosage was

adjusted "to obtain maximum benefit without side-effects." Nevertheless, side-effects and complications were noted, and, in particular, the incidence of "moon-face" was much higher in the prednisone group. In view of this, the more favourable results observed with prednisone may be due, in part at least, to the use of a dosage relatively high in comparison with that given in the form of cortisone. Further observations, now being made, are necessary before final conclusions can be drawn.

Medical Memorandum

Desensitization of a Nurse to Streptomycin under Corticosteroid Cover

In individuals who have become sensitized to streptomycin by handling it during their work, reactions to even ephemeral contact with the drug may become severe and disabling. It is possible to desensitize these people by giving increasing small doses of the drug parenterally; but in those with extreme sensitivity this may be very difficult and take several months to accomplish (Crofton, 1953; Cohen, 1954). Though hypersensitivity reactions may occur in patients being treated with streptomycin, these are not usually precipitated by such minute quantities as with streptomycin-handlers, and desensitization is usually easy (Crofton, 1953). When severe reactions are met in such patients, corticotrophin has been of great value in suppression (Houghton, 1954).

It should be particularly useful to give corticotrophin or corticosteroids while desensitizing streptomycin-handlers, who are so much more sensitive to the drug. I have seen no previous report of such use, though in the case described below it was clearly of the greatest benefit.

CASE REPORT

A female nurse aged 27 had had no previous episodes of allergy. For 18 months she had daily prepared and administered injections of streptomycin and declared that during these she had always taken the strictest precautions against personal contact (Crofton and Foreman, 1948). At the end of this period she began to experience severe soreness of the eyes and of the eyelids, with swelling of the latter, whenever she came near open solutions of streptomycin or even near a room where these injections had been given. A patch test was negative, but when 25 μ g of streptomycin sulphate was injected intradermally she soon developed local oedema 5 cm. in maximum diameter, with more widespread redness and soreness. Six hours later there was marked redness and soreness of both eyes and lids. When 2.5 μ g. was given intramuscularly there was an almost equally severe reaction in both eyes. She was then put on chlorpheniramine maleate, 4 mg. twice daily, and then 0.5 μ g. of streptomycin sulphate was given, but was followed six hours later by the same reaction. The chlorpheniramine maleate was continued and 0.25 μ g. of streptomycin sulphate given mixed in a solution containing 25 mg. of mepyramine maleate. A slightly less severe reaction occurred, but even with 0.1 μ g. it was still marked. At this point the nurse had become despondent, and it was obvious that, even if a smaller dose had been found where no reaction occurred, desensitization would have taken several months and would probably have been very difficult.

She was therefore admitted to sick-bay and prednisolone treatment started with 20 mg. daily—5 mg. being given at 7 a.m., 10 mg. soon after the streptomycin injection in order to achieve a peak concentration at the time when a reaction might be expected, and the remaining 5 mg. at 8 p.m. As she had arrested pulmonary tuberculosis, successfully

treated by artificial pneumothorax from 1937 to 1941, she was given 10 g. of para-aminosalicylic acid and 200 mg. of isoniazid daily, in two divided doses, as a precaution against reactivation of the tuberculosis.

The next day 1 μ g. of streptomycin was given intramuscularly without reaction. The day after, 2 μ g. was given without reaction, but with 4 μ g. there was slight redness of both upper eyelids. The following day 4 μ g. was given again without reaction, but with the next dose of 8 μ g. there was again slight redness. Next day, with 15 μ g., there was no reaction, and the dose was doubled daily until, with 120 μ g., there was redness again of the eyelids, which did not reappear, however, when this dose was repeated the following day (the 10th). The dose was then doubled daily until the 15th day, when with 2 mg. there was again slight redness of the lids. On repeating this quantity next day there was no reaction and the dose continued to be doubled daily. After 80 mg. a few tiny follicles appeared over the face and both legs, but these cleared after a few hours; there was no redness of the eyelids. After 150 mg., and again after 300 mg., there was a similar but more marked transient rash with pruritus. There was no rash after 500 mg., but some generalized pruritus. After 1 g. on the 25th day there was headache and slight erythema of both upper eyelids.

Because of these reactions, although they were mild, it was decided that the nurse was not yet completely desensitized. The prednisolone was increased to 25 mg. daily, the extra 5 mg. being given at 8 a.m. On the 26th day there was no reaction with 0.5 g. of streptomycin; the day after 0.6 g. was given without incident, as were 0.75 g., 0.9 g., and finally 1 g. on the 30th day. The nurse resumed full duties next day, including the preparation and administration of streptomycin injections. Streptomycin was continued in the dosage of 1 g. daily for a further 23 days to maintain the desensitized state, while the prednisolone was reduced by 5 mg. every three days until, after 12 days, it was discontinued after a total of 32 days; the last 11 injections of streptomycin were therefore given without any cover. There has been no reaction whatever to the injections, nor has daily contact with streptomycin preparations over the succeeding two months produced any of the former manifestations of sensitivity.

COMMENT

It is clear that in this case desensitization without corticosteroids would have been most complicated and might have taken several months. When prednisolone was given desensitization was rapid and comparatively uneventful. Possibly the quantities of streptomycin were increased too rapidly after 1 mg. or so, because there were slight manifestations of sensitivity from 80 mg. to 1 g.; these, however, did not reappear when 0.5 g. was given later, and after four doses of increasing size 1 g. was reached and maintained uneventfully. It was striking how well the nurse looked and felt during the whole course of desensitization once the prednisolone was begun; this was in contrast to the malaise and despondency caused by the reactions to test doses of streptomycin previously.

In streptomycin-handlers with marked hypersensitivity to the drug it is possible that desensitization may be greatly eased and speeded by suppressing sensitivity reactions with corticosteroids.

I am grateful to Professor J. W. Crofton for his guidance in this case.

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